UNIVERSITY OF UTAH
COLLEGE OF PHARMACY
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UTAH MEDICAID DUR REPORT
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BOTULINUM TOXIN

OnabotulinumtoxinA (*Botox*, *Botox Cosmetic*)
AbobotulinumtoxinA (*Dysport*)
IncobotulinumtoxinA (*Xeomin*)
RimabotulinumtoxinB (*Myobloc)*

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Contents

Background

Botulinum toxin is produced by the gram-positive spore-forming rod bacterium, *Clostridium botulinum,* under anaerobic conditions (where there is no oxygen). The endospores produced by the bacterium are found in soil and water. Botulinum toxin is very toxic when it reaches the systemic circulation. The illness caused by botulinum toxin is known as botulism. The toxin inhibits acetylcholine release and causes paralysis (neuromuscular blockage) without affecting mental status. The muscle weakness first affects the cranial nerves causing double vision, drooping of eyelids, loss of facial expression and swallowing problems, and then spreads to the arms and legs. It can also affect the autonomic nervous system which may cause dry mouth and throat, constipation, and postural hypotension. Severe cases may include respiratory depression and death without timely medical treatment.[2,3]

Botulism is rare, as it is unusual for people to get sick from the bacterium even though it is found naturally in many places. "In 2015, there were 199 cases of laboratory-confirmed botulism reported to the CDC."[2] The most well-known form of botulism in the US is infant botulism, thought to be acquired mostly from the natural environment. Some cases are thought to be linked to contaminated honey, hence the warning not to give honey to babies under 1 year old because their intestinal flora cannot suppress the growth of *C. botulinum* yet. In 2015, 141 out of the 199 cases of botulism were infant botulism. Botulism can also be contracted via food contaminated with *C. botulinum* spores especially in low-oxygen conditions, such as home-canned foods, which allow the spores to germinate. In 2015, 39 out of the 199 cases were foodborne (foods containing pre-formed botulinum toxin). Other cases of botulism include contaminated wounds (including those of illicit drug users), isolated cases of inhalation in laboratory workers, and inappropriate strengths of the pharmaceutical drugs injected for cosmetic or medical use (iatrogenic botulism).[2,3] Children, people who weigh less than a typical adult, and people with neuromuscular conditions are at increased risk for iatrogenic botulism. Of the 199 confirmed cases in 2015, 15 were cases of wound botulism (14 of these 15 were people who inject drugs), and 4 cases were of unknown/"other" etiology (other is defined as "A clinically compatible case that is laboratory-confirmed in a patient aged greater than or equal to 1 year who has no history of ingestion of suspect food and has no wounds").[2,4] The definition for this category also includes iatrogenic botulism and adult intestinal colonization (adult intestinal toxemia) botulism, "a rare kind of botulism that occurs among adults by the same route as infant botulism."[4]

Initial diagnosis is based on clinical symptoms, and it is recommended to start treatment without waiting for laboratory confirmation. "Laboratory confirmation is done by demonstrating the presence of botulinum toxin in serum, stool, or food, or by culturing *C. botulinum*, *C. butyricum*, or *C. baratii* from stool, a wound, or food."[2]

Botulism is treated with antitoxin, which prevents progression of paralysis, and the necessary supportive treatment (e.g., ventilator). Recovery may take weeks to months in severe cases and is dependent on the time required for regeneration of new neuromuscular connections, because the antitoxin does not reverse paralysis. With the improvements in medical care, more than 95% of people with botulism survive.[2]

The Utah Poison Control Center provided information on access to the antitoxins: Botulism antitoxin is available through the Centers for Disease Control and Prevention (CDC) on request of the state health department. Decisions to administer antitoxin are made in consultation among treating clinician, state health department, and the CDC. Infant botulism is treated with botulism immune globulin available through the California Department of Health at the request of the treating physician.

Currently, there are four Food and Drug Administration (FDA)-approved botulinum toxin products: three of botulinum toxin serotype A and one of serotype B.[5] Botulinum F toxin is still in investigational status.[6] Small doses of botulinum toxin products are injected into specific muscles, causing a temporary block of muscle function (muscle paralysis), to treat conditions such as cervical dystonia, spasticity, or blepharospasm. These products can also be used to control excessive salivary secretion. For example, when the products are used to block presynaptic acetylcholine release, the release of acetylcholine from cholinergic nerve endings is inhibited, leading to inactivity of muscles or glands.[7]

The main focus of this report is on off-label use in pediatrics for spasticity and sialorrhea (also called hypersalivation, drooling, or ptyalism).

1. The evidence-based standard of care for use in pediatrics for these 2 conditions
2. Recommendations on length of therapy and frequency of therapy based on the evidence found

According to Tilton et al., the dilemma of whether and how to medically treat spasticity in children is frequently faced by many clinicians.[8]

Spasticity and sialorrhea overview

The most common cause of spasticity in children is cerebral palsy (CP), but it could also be caused by congenital conditions, traumatic brain or spinal cord injuries, central nervous system tumors, metabolic disorders, and hydrocephalus.[8,9] Based on population studies, the CDC reports prevalence estimates of CP ranging from 1.5 to more than 4 per 1,000 live births or children of a defined age range.[10] The CDC tracks CP through the Autism and Developmental Disabilities Monitoring (ADDM) CP Network. According to a 2008 ADDM CP Network report on 8-year-old children living in areas of Alabama, Georgia, Missouri, and Wisconsin, CP was more common among boys than among girls, and more common in black children than white children (Hispanic and white were equally likely). Most (77.4%) of these children with CP had spastic CP.[10] Spasticity affects daily activities and can be painful. Treatment of spasticity requires a careful pretreatment assessment using valid and reliable clinical instruments so that the most appropriate treatment options are selected. Also, "…importantly, specific, measurable, achievable, and realistic treatment goals should be delineated." Treatment options mentioned in general in the literature include pharmacological (e.g., baclofen, clonidine, tizanidine, botulinum toxin) and non-pharmacological interventions (e.g., casting splints and stretches).[11] In patients with brain injuries, behavioral and cognitive issues associated with the injuries may complicate matters.[11]

Drooling (sialorrhoea) is often experienced by patients with cerebral palsy due to oromotor dysfunction.[12] According to various sources, it occurs in 10-80% of patients with paediatric cerebral palsy.[13] Drooling is caused by hypersalivation or oral motor dysfunction and may also occur in patients with neurological disease (e.g., amyotrophic lateral sclerosis or Parkinson disease), brain injury, multiple sclerosis, cerebrovascular disease, intellectual disability, oromandibular carcinoma, or abnormalities of the jaw, lips or oral cavity.[7,14] Drooling can impact health and quality of life.[7] Patients may experience skin irritation or rashes in the areas around the mouth, mouth infections, dehydration, interference with speech, and can develop pneumonia because of difficulty swallowing and aspiration.[7,12] Drooling has a huge impact on interpersonal relationships and integration into society.[7] Treatment and management of drooling includes suction, oral drug treatment (e.g., anticholinergics), surgical procedures (e.g., surgical excision of the salivary glands or salivary duct rerouting or ligation of the salivary glands), radiotherapy, and botulinum toxin injections.[13] Other interventions used to reduce or eliminate drooling include

"physical therapies, therapies to improve sensory function, behavioral therapies to assist the child in managing his/her own drooling, appliances placed in the mouth, and acupuncture."[12]

Methodology

Micromedex, Lexicomp, and the product labels were first searched for FDA-approved, off-label use and product information.

Cochrane Library literature searches for systematic reviews were conducted. Medline (PubMed), Up to Date, the Agency for Healthcare Research and Quality (AHRQ), the U.S. Department of Health and Human Services website, the FDA website, The American Academy of Neurology (AAN) website, Micromedex, and Lexicomp were searched for safety information, systematic reviews, clinical trials, and other guidelines. References of relevant search results were screened.

Botulinum toxin products and indications

Table 1. FDA-approved indications of botulinum toxin agents[1,6,15-17]

	Considered Medical Uses									Cosmetic Uses (moderate to severe)		
FDA-approved age	≥18	≥18	≥2	≥18	≥18	≥12	≥12	≥18	≥18	≥18 (Dysport <65)		
Product / **Indication**	Cervical Dystonia (spasmodic torticollis)	Spasticity[a]	Spasticity	Overactive bladder[b]	Urinary incontinence[c]	Blepharospasm associated with dystonia	Strabismus	Migraine (chronic[d]) prophylaxis	Axillary hyperhidrosis (severe)	Glabellar lines[e]	Lateral canthal lines	Forehead lines
OnabotulinumtoxinA (Botox)	✔ O	✔	O[f]	✔	✔	✔ O	✔ O	✔	✔			
Requirement for inadequate response or intolerance to other agent first				YES: Anticholinergic					YES: Topical agents			
OnabotulinumtoxinA (Botox Cosmetic)										✔	✔	✔
AbobotulinumtoxinA (Dysport)	✔ O	✔	✔ (lower limb) O[f]			O				✔		
Requirement for inadequate response or intolerance to other agent first												
IncobotulinumtoxinA (Xeomin)	✔	✔ (upper limb)				✔				✔		
Requirement for inadequate response or intolerance to/treatment with other agent first/before						YES: Botox						
Rimabotulinumtoxin B (Myobloc)	✔ O											
Requirement for inadequate response or intolerance to other agent first												

O=Orphan designation

[a]Note product labels contain information specifically about safety and effectiveness in specific upper and lower limb muscles. Product labels state: *"Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins."*

[b]with symptoms of urge urinary incontinence, urgency, or frequency

[c]due to detrusor overactivity associated with a neurologic condition e.g. spinal cord injury or Multiple Sclerosis

[d]Chronic is defined as ≥15 days per month with headache lasting 4 hours a day or longer

[e]frown lines between eyebrows associated with corrugator and/or procerus muscle activity (temporary improvement). Note that Micromedex lists this indication as "Wrinkled face (Moderate to Severe), Hyperfunctional'" in adults younger than 65 years.

[f] Treatment of dynamic muscle contracture in pediatric cerebral palsy patients

Botox has the most FDA-approved indications, but it is important to consider the LIMITATIONS OF USE listed in the product label (Safety and effectiveness of BOTOX have not been established for):

- Prophylaxis of episodic migraine defined as ≤14 headaches per month
- Spasticity in pediatric patients (upper and lower)
- Hyperhydrosis in other areas of the body than axillary

AbobotulinumtoxinA (Dysport) is the only botulinum toxin product that is FDA-approved for use in spasticity in pediatrics, and this is limited to lower limb spasticity. Note that the product label states that the safety and effectiveness of abobotulinumtoxinA to treat the proximal muscles of the lower limb in pediatric patients have not been evaluated.

Sialorrhea is an off-label use for all products, and off-label information for this use has only been included for adults in Micromedex and Lexicomp.

Micromedex includes 2 studies as evidence for use of abobotulinumtoxinA in lower limb spasticity in children. A randomized study (n=235) was performed in children with cerebral palsy (2 to 17 years) with lower limb spasticity causing dynamic equinus foot deformity. AbobotulinumtoxinA was injected into the gastrocnemius and soleus muscles, and researchers found significantly improved mean change in ankle plantar flexor muscle tone and Physician's Global Assessment compared with placebo at week 4 and at week 12. The other study was a small randomized study (n=40) where researchers found significantly improved walking patterns in children with lower limb-spastic cerebral palsy (ages 2 to 16 years).[15,18,19] However, in another small study (n=52), researchers did not find a significantly improved walking pattern in children with lower limb-spastic cerebral palsy (ages 2 to 7 years), though the possibility that it may have been underpowered is mentioned.[19,20]

Botox, Dysport, and Myobloc have orphan drug designations. Currently, only some of these orphan drug designations are FDA approved (specific to the product; designations not FDA approved are italicized): Botox orphan drug designations for treatment of strabismus and blepharospasms, cervical dystonia, and *dynamic muscle contracture in pediatric cerebral palsy patients* (not FDA-approved);[21] Dysport for treatment of *blepharospasm* (not FDA-approved), cervical dystonia, and dynamic muscle contractures in pediatric cerebral palsy patients (FDA-approval for lower limb);[19] and Myobloc for cervical dystonia.[22]

Off-label use evidence (Micromedex and Lexicomp) and Canadian additional use (not in US labeling)

The main focus of this report is on off-label use in pediatrics for spasticity and sialorrhea (also called hypersalivation or ptyalism), but off-label use evidence in general from Micromedex and Lexicomp is summarized in this section for adults and pediatrics to provide a better overview of the products and to ensure that off-label use related to spasticity and sialorrhea in children is not overlooked.

The information in the first two columns of Table 2 contains approved uses specific to Canada.

The Canadian labeling includes:

- Dynamic equinus foot deformity in pediatric cerebral palsy patients for Botox
- A broad indication for Xeomin: "Treatment of hypertonicity disorders of the seventh nerve (e.g., blepharospasm, hemifacial spasm) in adults."[23] In the US, Xeomin is FDA-approved for blepharospasm only, and it is for use in patients previously treated with onabotulinumtoxinA (Botox). All FDA-approved indications for Xeomin are in adults; other FDA-approved indications are for use in cervical dystonia, upper limb spasticity, and glabellar lines.

Table 2 contains a summary of the level/strength of evidence assessment from Micromedex. The table is followed by the definitions for Micromedex efficacy, strength of evidence and strength of recommendation.

Micromedex only includes two off-label uses in pediatrics in their 'quick answers' list for Botox where evidence favors efficacy:

- spasticity associated with cerebral palsy
- hypersalivation associated with disorders of the central nervous system.

Both these off-label uses have class IIb recommendations meaning that it may be useful, and is indicated in some, but not most, cases.[21] There are no pediatric off-label uses listed for any of the other botulinum toxin products in the quick answer lists in Micromedex.

Cerebral Palsy

Use of botulinum toxin in children with cerebral palsy appears to be for equinus of the ankle due to increased gastrocnemius/soleus muscle tone, and to improve upper extremity function in children with hemiplegic cerebral palsy. The evidence for onabotulinumtoxinA (Botox) use in cerebral palsy was based on 3 studies that evaluated the safety and efficacy of Botox for the following:

Equinus of the ankle:

A. Short-term (3-month): A small (n=114) prospective, randomized, double-blind, placebo-controlled trial evaluated the safety and short-term efficacy of Botox injections.[24] The authors reported "improved dynamic gait pattern and active range of motion (ROM) in patients with lower limb spasticity due to cerebral palsy", and "no serious adverse events were reported."[21,24]
B. Long-term (over a 2 year period; mean duration of BTX-A exposure was 1.46 years per patient): A prospective, open-label, multicenter (9 centers) clinical trial evaluated repeated intramuscular injections of BTX-A (given approximately every 3 months).[25] The authors concluded that it is a safe and effective treatment option in these patients based on improved dynamic gait patterns and no serious adverse events reported.[21,25]
   NOTE: "Nine investigators enrolled 207 patients, combining 131 patients from the preceding randomized, double-blind trial with an additional 76 new patients."

AND

Upper extremity function in children with hemiplegic cerebral palsy:

C. Efficacy was demonstrated in a small (n=30; 29 completed study) randomized, single-blind, controlled trial of onabotulinumtoxinA plus occupational therapy in hemiplegic children (2.5 to 10 years old) with spastic cerebral palsy.[26] The Botox injections were administered into 1 or more of 3 muscle groups (biceps, volar forearm muscles, adductor pollicis). The authors reported improved upper limb function (measured by the Quality of Upper Extremities Test [QUEST]) compared with OT-alone and concludes that it supports the effectiveness of this treatment option in these children with at least moderate spasticity.[21,26]

Table 2. Micromedex listed off-label uses and Canadian-specific indications (not FDA approved) of botulinum toxin agents[6,23]

	Canada		Micromedex																										
Product	Equinus foot deformity in pediatric cerebral palsy patients	Hypertonicity disorders of the seventh nerve (eg, blepharospasm, hemifacial spasm)	Cerebral palsy - Spasticity	Gilles de la Tourette's syndrome	Blepharospasm	Hemifacial spasm	Achalasia*	- Disorder of esophagus - Pharyngoesophageal segment spasm – total laryngectomy	Auriculotemporal syndrome	Disorder of NS- Excessive salivation	Excessive salivation, Medical condition-associated; Prophylaxis	Excessive salivation - Parkinson's disease, Advanced	- Difficulty speaking - Total laryngectomy - Spastic dysphonia - Organic voice tremor	Granuloma of vocal cords, Refractory to conventional surgical and medical therapies	Idiopathic trigeminal neuralgia, Refractory	Epicondylitis (tennis elbow)	Fibromyalgia	Cervicogenic headache	Backache	Benign prostatic hyperplasia	Isolated oromandibular dystonia	Larynx closure, adjunct to syrgical procedure	Temporomandibular joint disorder	Tardive dyskinesia	Whiplash injury to neck	Pelvic floor dyssynergia	Bladder muscle dysfunction - overactive	Wrinkled face, Hyperfunctional
Botox **OnabotulinumtoxinA**				✔ IIb B	FDA	✔ IIa B	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B		✔ IIa B	✔ IIb B	✔ IIb C	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb C	✔ IIb B	✔ IIb B	✔ IIb B	✔ IIb B		
Pediatric use	✔		O ✔ IIb B							✔ IIb B																		
Dysport **AbobotulinumtoxinA**					O ✔ IIa B	✔ IIb B																						
Pediatric use			O FDA†		O																							
Xeomin **IncobotulinumtoxinA**		✔			FDA																							
Pediatric use																												
Myobloc **RimabotulinumtoxinB**											✔ IIb B															✔ IIb B	✔ IIb B
Pediatric use																												

FDA=FDA-approved
O=Orphan designation
*Achalasia is a rare swallowing disorder due to where the muscles in the esophagus do not contract normally and the lower esophageal sphincter does not function correctly which is caused by degenerated nerve cells for which the cause is unknown.[27]
NS=Nervous System
Micromedex includes additional information in the detailed summaries for other off-label conditions. Only the off-label uses listed in the quick answers have been included in the table above.
† Treatment of lower limb spasticity in pediatric patients ≥2 years.

MICROMEDEX

"Class I - Recommended

- The given test or treatment has been proven to be useful, and should be performed or administered.

Class IIa - Recommended, In Most Cases

- The given test, or treatment is generally considered to be useful, and is indicated in most cases.

Class IIb - Recommended, In Some Cases

- The given test, or treatment may be useful, and is indicated in some, but not most, cases.

Class III - Not Recommended

- The given test, or treatment is not useful, and should be avoided.

Class Indeterminate - Evidence Inconclusive"

"Category A

- Category A evidence is based on data derived from: Meta-analyses of randomized controlled trials with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.

Category B

- Category B evidence is based on data derived from: Meta-analyses of randomized controlled trials with conflicting conclusions with regard to the directions and degrees of results between individual studies. Randomized controlled trials that involved small numbers of patients or had significant methodological flaws (e.g., bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (e.g., cohort studies, case-control studies, observational studies).

Category C

- Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.

No Evidence"

Efficacy (Excerpt)		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective
Class IIa	Evidence Favors Efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is Inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

Apart from the conditions listed in the table above, the following uses are also listed in Micromedex as off-label (non-FDA) uses for onabotulinumtoxinA, but the evidence is inconclusive:[21]

- Anal fissure, chronic
- Congenital esotropia
- Detrusor and sphincter dyssynergia
- Essential tremor
- Excessive tear production
- Hemorrhoidectomy - Postoperative pain
- Injury to oculomotor nerve (acute)
- Migraine, episodic; prophylaxis
- Stuttering
- Tension-type headache
- Thoracic outlet syndrome

Lexicomp has spasticity of cerebral palsy included as an off-label use for Dysport in their off-label use section, but their information is dated 2010. Their FDA-approved section includes the recent (2016) FDA-approval for treatment of lower limb spasticity in pediatric patients ≥2 years. Spasticity of cerebral palsy is mentioned as an off-label use for Botox, but an evidence scale rating is not provided.

Table 3. Lexicomp listed off-label uses of botulinum toxin agents[28]

	Adults							Pediatric
Product	Achalasia	Anal fissures	Sialorrhea (drooling)	Tardive dyskinesia	Acquired nystagmus	Hand dystonia	Upper limb spasticity (adults)	Spasticity of cerebral palsy (children/adolescents)
OnabotulinumtoxinA (Botox)*	B G-1	B G-2	B G-3	C				
AbobotulinumtoxinA (Dysport)		A G-2	B G-3	C	C	C		A G-4
IncobotulinumtoxinA (Xeomin)			B G-3					
RimabotulinumtoxinB (Myobloc)◊			B G-3				G-5	

* Other off-label uses mentioned for Botox: “Dynamic muscle contracture in pediatric cerebral palsy patients; Oromandibular dystonia; Spasmodic dysphonia (laryngeal dystonia) and other dystonias (ie, writer's cramp, focal task-specific dystonias)”[29]

1. American College of Gastroenterology (ACG) guidelines: Botulinum toxin is recommended for “patients with achalasia who are not candidates for pneumatic dilation or surgical myotomy, based on moderate-quality evidence.”[29]
2. Evidence-based guidelines (Association of Coloproctology of Great Britain and Ireland[30], Evidence-based treatment algorithm[31]) “recommend botulinum toxin A IM injection as an option for the treatment of anal fissures in adults who have not responded to preferred therapy.”[29]
3. Refer to guideline section
4. Refer to guideline section
5. American Academy of Neurology practice guidelines on the use of botulinum neurotoxin: “RimabotulinumtoxinB may be considered as a treatment option for focal manifestations of adult upper limb spasticity.”[32]

LEXICOMP

“Level of Evidence Scale
A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.”

Safety

According to the 2010 practice parameter from the AAN and Child Neurology Society for the treatment of spasticity in children and adolescents with cerebral palsy, specific adverse effects were reported in 17 studies (involving botulinum A) and the most common were "localized pain, excessive weakness, unsteadiness and increased falls, and fatigue." In addition there were a few reports of urinary incontinence (5 patients) and dysphagia (2 patients). All these adverse effects reported were described as transient and did not require hospitalization.[33] Based on the evidence, the authors found that botulinum A appeared generally safe in children with cerebral palsy, but mentioned the potential for generalized weakness to occur.[33]

Black Box warning

"WARNING: DISTANT SPREAD OF TOXIN EFFECT
Postmarketing reports indicate that the effects of [BOTOX April 2017; DYSPORT June 2017; MYOBLOC May 2010; Xeomin Dec 2015] and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, [blurred vision; Xeomin; Myobloc; Dysport], ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including [upper limb; Dysport] spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to [those used to treat cervical dystonia and spasticity and at lower doses; Botox]; [those used to treat cervical dystonia and spasticity and at lower doses; Myobloc] [those used to treat cervical dystonia and spasticity and at lower doses; Xeomin]; [or lower than the maximum recommended total dose; Dysport]."[1]

Figure 1

There are some differences in the black box warning between the different botulinum toxin product labels.

The labels for all four products include diplopia (double vision) as botulinum toxin effects, and the labels for three of the products (all except Botox) include blurred vision.

The Dysport label includes upper limb spasticity in children when referring to the unapproved uses, whereas the other labels state, more generally, spasticity in children as an off-label use. Dysport is the only product that is approved for spasticity in children, but only for lower limb spasticity, which is the reason for this difference.

The other difference noted was the wording for doses when spread of effect was seen, which is also related to the FDA-approved indications.

Comparison of botulinum toxin formulations

Botulinum toxin products are not interchangeable because the units of activity are unique to each product, and different doses are recommended for each product.

Table 4. Pediatric dosing information (adapted from Lexicomp)[28]

Product	Dosage Forms and Strengths Available	Pediatric dosing information for spasticity or hypersalivation[34]	Recommended maximum dose	Recommended frequency
OnabotulinumtoxinA (Botox)	**Injection, powder for solution:** *Botox:* 100 and 200 units *Botox Cosmetic:* 50 and 100 units	Not FDA approved for either indication Canadian labeling Spasticity (cerebral palsy related [dynamic equinus foot deformity]) Botox: Children ≥2 years: IM: 4 units/kg (total dose) divided into two injections into medial and lateral heads of the gastrocnemius of affected leg	*400 units in 3 month interval* *Canadian labeling: 200 units* *Diplegia: 6 units/kg (total dose) divided between affected limbs*	*Canadian labeling: if clinically indicated, may repeat every 2 months*
AbobotulinumtoxinA (Dysport)	**Injection, powder for solution:** 300 and 500 units	Not FDA approved for hypersalivation FDA-approved for lower limb spasticity (≥2 years) "Individualize dose based on patient size, number and location of muscles involved, severity of spasticity, local muscle weakness, response to prior treatment and/or adverse reaction history." Total dose per treatment session: 10 to 15 units/kg per limb. Divide total dose administered between the affected muscles; distribute dose across >1 injection site in any single muscle if possible; Recommended dose range per muscle per limb: Gastrocnemius: 6 to 9 units/kg (up to 4 injections per muscle per limb) Soleus: 4 to 6 units/kg (up to 2 injections per muscle per limb)"[34]	Per treatment session: "15 units/kg for unilateral injections, 30 units/kg for bilateral injections, or 1,000 units, whichever is less." NOT >0.5 mL in any single injection site.	No more frequently than every 12 weeks/3months "In clinical studies, the majority of patients were re-treated between 16 to 22 weeks; however, some patients had a longer duration of response."
IncobotulinumtoxinA (Xeomin)	**Injection, powder for solution:** 50, 100, and 200 units	Not FDA-approved for either indication and no pediatric use information or dosing information in Lexicomp		
RimabotulinumtoxinB (Myobloc)	**Injection, solution:** 2,500 units per 0.5 mL; 5,000 units per 1 mL; 10,000 units per 2 mL	Not FDA-approved for either indication and Lexicomp states 'Not established in pediatric patients' for dosing information		

According to the 2010 practice parameter from the AAN and Child Neurology Society for the treatment of spasticity in children and adolescents with cerebral palsy, some experts recommend using the smallest dose of botulinum toxin A and avoiding injecting more frequently than every 3 months to minimize the risk of antibody resistance.[33,35] From a safety perspective this is also a good recommendation to minimize the potential for adverse outcomes.

Risk factors that increase risk of adverse events

- Children treated for spasticity[1,15-17]
- Patients with underlying conditions that would predispose them to botulinum toxin effects/symptoms[1,15-17]

Utah Poison Control Center (UPCC)

Appendix 2 contains a summary of the cases over the last 5 years involving Botulinum Toxin Type A from the Utah Poison Control Center (UPCC). They had a total of 16 cases (all adults); 13 of these were concerns for adverse effects following injection. They reported that the therapeutic reason for the injection was not clear in many cases, but included migraine headaches in 2, forehead wrinkles in 1 and excessive sweating in another. Patients that sought medical treatment in a hospital or clinic were discharged from the emergency department/clinic, and one was admitted overnight for observation. Viral illness was suspected in several cases. None of these cases resulted in botulism.

Appendix 3 contains a summary of the botulism exposures in the last 5 years from the Utah Poison Control Center (UPCC). There were 9 cases in the last 5 years, and sources were environmental (infant), homemade alcohol, and beets. None of the cases were iatrogenic (caused by pharmaceutical botulinum toxin products).

Clinical Guidelines

Table 5 summarizes the current clinical practice guidelines available for the treatment of spasticity in children.

The 2010 Practice Parameter from the American Academy of Neurology and the Child Neurology Society recommends that Botulinum toxin A be offered for localized spasticity that warrants treatment.[33] The guidance does not appear to distinguish between the different botulinum toxin products. They do state that different formulations are not bioequivalent and may have different efficacy and safety profiles after mentioning that BoNT-A is approved for this indication in Canada. At that time botulinum toxin A was not FDA-approved for use in spasticity in children and currently, it is only Dysport that is FDA-approved for use in lower limb spasticity in children ≥2 years old.

Not all patients would benefit from spasticity reduction and some may experience a decline in function. The authors of the practice parameter therefore state that this needs to be a decision based on a careful assessment of the patient's other impairments such as movement disorders and weakness, the type of treatment and use thereof.[33] They also list reasons for treatment of spasticity:

- To reduce pain and muscle spasms
- To facilitate brace use
- To improve posture
- To minimize contractures and deformity
- To facilitate mobility and dexterity
- To improve patient ease of care and hygiene/self-care[33]

When this evidence-based review was conducted, botulinum toxin A was considered an effective treatment to reduce spasticity in upper and lower extremities, but there was conflicting evidence regarding functional improvement. More evidence was also needed on ease of caregiving, activity, participation, safety and long-term effects.[33]

Table 5. Clinical Guidance for the Treatment of Spasticity in Children

Guideline	Recommendations
2010 Practice parameter from the American Academy of Neurology (AAN) and the Child Neurology Society.[33] Pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review; literature search 1966 to July 2008) **Current guideline. Reaffirmed on July 13, 2013.[36]**	"For localized/segmental spasticity that warrants treatment, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A)." There are insufficient data to support or refute the use of phenol, alcohol, or botulinum toxin type B (Level U). For generalized spasticity that warrants treatment, diazepam should be considered for short-term treatment, with caution regarding toxicity (Level B), and tizanidine may be considered (Level C). There are insufficient data to support or refute use of dantrolene, oral baclofen, or continuous intrathecal baclofen (Level U)."
2008 Assessment: Botulinum neurotoxin (BoNT) for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.	"Botulinum neurotoxin should be offered as a treatment option for the treatment of spasticity in adults and children (Level A)."[37] AAN Summary of Evidence-based Guideline for Clinicians RECOMMENDATIONS FOR THE USE OF BoNT IN CHILDREN WITH SPASTICITY DUE TO CEREBRAL PALSY "Strong evidence supports Injection of BoNT into calf muscles as a treatment option for equinus varus deformity in children with CP (Level A). Good evidence supports Consideration of BoNT as a treatment option of thigh adductor spasticity and for pain control undergoing adductor-lengthening surgery (Level B). Good evidence supports Injection of BoNT as a treatment option for children with upper extremity spasticity (Level B). Clinical context Though clinicians, patients, and caregivers have found BoNT treatment for spasticity gratifying, the United States Food and Drug Administration has not approved BoNT for the treatment of spasticity in children or adults."[38]

*"Classification of Recommendations: A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)** B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.) C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.) U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. **In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2)."[39]*

"AAN Classification of Evidence for Therapeutic Intervention: Class I: Randomized, controlled clinical trial with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: (a) concealed allocation; (b) primary outcome(s) clearly defined; (c) exclusion/inclusion criteria clearly defined; and (d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently

*low to have minimal potential for bias. Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a RCT in a representative population that lacks one criteria a-d. Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.** Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report."*[38]

Table 6 summarizes the current clinical practice guidance available for the treatment of sialorrhea in children.

The international consensus statement recommend that the least invasive therapies appropriate for the patient should be selected taking into account the wishes of the individual and their caretaker. Careful assessment is required prior to the injection of botulinum toxin A in patients with cerebral palsy or dysphagia, and that potential side effects should be discussed with the patient and caretaker.

Table 6. Guidelines for the treatment of sialorrhea in children

Guideline	Population	Recommendations	Guideline level of evidence recommendation
2010 *International consensus statement*[7] (in response to clinical questions raised at the International Botulinum Neurotoxin Consensus Workshop)	Pediatric and adult patients with drooling	"Botulinum neurotoxin type A injection is recommended for administration into the salivary glands (parotid and submandibular), ideally under ultrasound guidance." "Various dosing ranges were provided based on product preparation (ie, *Botox*, *Dysport*, *Myobloc*) and injection site (ie, submandibular gland, parotid gland)."	Expert opinion Class I: Several prospective controlled clinical trials for botulinum toxin A and B.
2013 Evidence-based review & update of 2008 report.[40] ***Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (2008)***	Botulinum neurotoxin in the treatment of autonomic disorders and pain (included children)	Refer to publication for complete information. This is only the recommendation for drooling: Level B recommendation for the use of A/Abo (Dysport), A/Ona (Botox), and B/Rima (Myobloc) and a Level U recommendation for A/Inco (Xeomin). (AAN classification scale included after table 5)	Evidence-based review[40] Eight trials in a total of 222 adults and children.

Table 7. Other Guidelines/Regulatory Safety updates

Guideline	Off-label indication	Population	Recommendations	Guideline level of evidence recommendation
2012 European Federation of Neurological Societies (EFNS) guidelines on the clinical management of Amyotrophic Lateral Sclerosis* (ALS)[41]	Sialorrhea (drooling)	Adults with ALS	Botulinum toxin A is recommended in patients refractory to first-line therapy to improve quality of life.	Level A, B, or C recommendations or classification as good clinical practice points (GCPP) 13 ALS cases in the literature evaluated. Good clinical practice points (GCPP): amitriptyline, hyoscine (scopolamine oral or transdermal), or sublingual atropine drops

Guideline	Off-label indication	Population	Recommendations	Guideline level of evidence recommendation
				Level B (1 RCT): Botulinum toxin B Level C (few weaker studies): Botulinum toxin A No data for glycopyrrolate
2008 American Academy of Neurology (AAN) report[42]	Sialorrhea (drooling)	Adults with Parkinson-related sialorhea	Botulinum toxin A is classified as probably safe and effective in Parkinson-related sialorrhea.	Quality of the study rating scale: Class I-IV. Recommendation based on 4 class II studies (3 using botulinum toxin A and 1 using botulinum toxin B)

*ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord and sialorrhea could be one or the symptoms of this disease.[43]

Systematic review evidence

Tables 1 and 2 in Appendix 1 contains information from relevant systematic reviews identified in the Cochrane Library.

Lower limb spasticity in cerebral palsy

Ade-Hall and Moore (Cochrane review; 2000) only found three small studies and concluded that there was insufficient evidence to support or refute the use of botulinum toxin A for the treatment of leg spasticity in cerebral palsy.[44]

Ryll et al. (Other review; 2011) included eight trials in a review assessing the effects of leg muscle botulinum toxin injections on walking in children with spasticity-related cerebral palsy. They conclude that the results should be interpreted with caution due to the limited quality, but that botulinum toxin with usual care or physiotherapy seems to improve walking in these children.[45]

Koog and Min (Other review; 2010) evaluated the effects of botulinum toxin on calf muscles in children with cerebral palsy and concluded "Although we found evidence supporting the efficacy of botulinum toxin A in studies comparing botulinum injection with non-sham controls, we did not find clear evidence of support in studies comparing botulinum injection with sham injection."[46]

Upper limb spasticity in spastic cerebral palsy

Hoare et al. (updated Cochrane review; 2010) report that they found high level evidence supporting the use of botulinum toxin A as an adjunct to occupational therapy for managing upper limb spasticity in children with cerebral palsy, but not for use of botulinum toxin alone (moderate evidence that it is ineffective alone).[47]

Drooling

Walshe et al. (Cochrane review; 2014) found insufficient evidence to determine the safety and effectiveness of botulinum toxin A (and benztropine and glycopyrrolate) for the treatment of drooling in

patients with cerebral palsy. The review included 4 studies evaluating botulinum toxin A and 2 evaluating benztropine and glycopyrrolate, but the authors report that there were methodological flaws associated with all of these studies.[12]

Vashishta et al. (Other review; 2013) included eight studies (181 patients) in their review and concluded "that botulinum toxin is a clinically effective therapy that improves drooling severity in patients with sialorrhea."[48]

Rodwell et al. (Other review; 2012) evaluated the effectiveness of botulinum toxin injections into salivary glands in children with cerebral palsy and neurodevelopmental disorders and included 16 trials in their review. The authors concluded that it is "an effective temporary treatment for sialorrhea in children with cerebral palsy", but they also warn that "benefits need to be weighed against the potential for serious adverse events" and that more safety and comparative studies with other treatment options are needed.[49]

Congenital talipes equinovarus (clubfoot)

Gray et al. (Cochrane review; 2014) only found one trial that reported on function (which was their main measure of success of treatment). The review includes findings of 3 trials on different plaster casting and the authors commented that data were not available to assess the results for adding "botulinum toxin A to the Ponseti treatment".[50]

Spasticity following traumatic brain injury

Synnot et al. (Cochrane review; 2017) found only 5 studies (105 participants) that assessed many different interventions. One study included children (n=25), but did not assess botulinum toxin. Overall, the authors concluded that the quality of the available evidence is very low and that there is insufficient evidence to determine the safety and efficacy of these interventions.[11]

Factors to consider

- **Pediatric dosing recommendations**
    - Refer to table 13
    - The black box warning for the potential for the botulinum toxin to spread from the area of injection to produce symptoms consistent with botulinum toxin effect should be considered (potential for severe generalized weakness)
    - Lexicomp states that the lowest recommended dose should be used when initiating treatment (regardless of indication).[29]
    - The different formulations are not bioequivalent and caution should be exercised in determining the appropriate dose.
    - "Canadian labeling (not in US labeling) recommends a maximum cumulative dose of 6 units/kg (up to 200 units) over 3 months in pediatric patients receiving treatment for more than 1 indication."[29]

Spasticity (cerebral palsy related [dynamic equinus foot deformity])

- Dysport is indicated for lower limb spasticity in children ≥2 years old.
- "Botox: *Canadian labeling (not approved in US labeling):* Children ≥2 years: IM: 4 units/kg (total dose) divided into two injections into medial and lateral heads of the gastrocnemius of affected leg; if clinically indicated, may repeat every 2 months (maximum dose: 200 units); in diplegia, the recommended dose is 6 units/kg (total dose) divided between affected limbs"[29]

- **Duration and frequency of use**

  The duration of response is the time until nerve terminal acetylcholine reaccumulates, which is typically 3 to 4 months.
  - Some experts and product labeling recommend dosing no more frequently than every 3 months.

- **Spasticity:** See dosing above (only Dysport FDA-approved for lower limb spasticity in children). Authors of a 2000 Cochrane review found insufficient evidence to support this use.[44] Authors of a more recent review (not a Cohrane review) found that it seems to improve walking in children with spasticity related cerebral palsy, but cautioned about the quality of evidence.[45] A 2010 Cochrane review found sufficient evidence for use of botulinum toxin A as an adjunct to occupational therapy for managing upper limb spasticity in children with cerebral palsy, but not for use of botulinum toxin alone. The AAN and Child Neurological Society recommend botulinum toxin A for localized or segmental spasticity as an effective and generally safe treatment, and states insufficient evidence for botulinum B.[33,36] Oral options are suggested for generalized spasticity (refer to table 5). Table 5 also includes information on equinus varus deformity in children with CP (strong evidence supports) and other evidence.

- **Drooling:** Botulinum toxin injections into the salivary glands for the treatment of drooling is an off-label use, and requires repeat injections.[51] Evidence is conflicting. A recent Cochrane review found insufficient evidence for this use and reports methodological flaws are associated with the available studies.[12] Authors of other reviews concluded that it is an effective therapy for drooling, but that it is temporary and that benefits need to be weighed against the potential serious adverse events.[48,49] The International consensus statement includes a recommendation for botulinum toxin A injection into the salivary gland based on expert opinion.[7] The AAN has a Level B recommendation (*Probably effective, ineffective or harmful)* for A/Abo, A/Ona, and B/Rima and a Level U recommendation (*Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven)* for A/Inco.

- **Other uses in children:** It is important to consider that this review focused on use of botulinum toxin in children in the treatment of spasticity or sialorrhea. However, it is possible that clinicians may be using botulinum toxin for other indications in children. For example, uses in non-ambulant children with CP could include managing pain, improving function in children with CP in Gross Motor Function Classification System (GMFCS) levels IV and V, maintaining hip integrity, achieving functional changes, and goal attainment.[52]

- **Misuse, abuse, or fraudulent products**: Botulinum toxin is classified as both a drug and biological product under federal law. There have been cases of botulism caused by use of unapproved Botulinum products and Botox fraud schemes. Botulinum toxin products for use in humans and distribution of botulinum toxin in any form for use in humans have to be FDA approved.[53]

- **FDA import alert**: In May 2017, the FDA issued a new import alert for botulinum toxin products, because of unlicensed botulinum toxin imports. The alert states that these products have been imported *"into the United States via international express mail services without proper declaration of contents by the sender. These shipments are small and are generally shipped cooled using a cold pack. Several foreign pharmacies have sent unlicensed product directly to physicians."* The new alert contains an additional legal charge for unlicensed Botulinum toxin, and *"districts may detain without physical examination the specified biologic products from the firms identified on this alert unless they are covered by a valid IND."* The list includes firms from Brazil, Canada, China, Dominican Republic, Hong Kong, and the United Kingdom. Firm names for example include the following references: scientific, medical, biotechnology, laboratories, depots, logistics, and pharmacies (these include pharmacies in London). The alert contains the currently approved U.S. products and U.S. license numbers as *"Only Botulinum toxin manufactured under U.S. license and bearing the U.S. license number on its labeling may be imported into the United States unless the unlicensed version has an Investigational New Drug (IND) application accepted by the Center for Drug Evaluation and Research."*[54]

Utah Medicaid Utilization Data

The utilization data in this section is presented as follows:

1) Total utilization data (All patients)
   a) Table showing total utilization by prescription claims and CPT codes and the combined total
   b) AGE AND SEX of patients for whom there were claims for botulinum toxin products
   c) The number of patients that received botulinum toxin that had select diagnosis codes or relevant CPT codes submitted
2) Pediatric utilization data
   a) Table showing total utilization by prescription claims and CPT codes and the combined total
   b) AGE AND SEX of patients for whom there were claims for botulinum toxin products
   c) The number of patients that received botulinum toxin that had select diagnosis codes or relevant CPT codes submitted
3) Pharmacy claims
   a) Table showing pharmacy claims for botulinum toxin products
   b) Prescriber details
4) Frequency of fills compared to recommendations (no more frequently than every 3 months)

1) Total utilization data (All patients)

a) Table showing total utilization by prescription claims (Rx) and CPT codes and the combined total unique patients

Botulinum toxin - RX CLAIMS

		2014		2015		2016		2017*		ALL		WITH CPT	
AGENT	**PRODUCT**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**	**CLAIMS**	**PATIENTS**
Abobotulinum-toxinA	DYSPORT INJ 300UNIT	181	72	132	56	80	35	67	35	**460**	**128**	144	66
Abobotulinum-toxinA	DYSPORT INJ 500UNIT	160	58	89	36	51	26	34	18	**334**	**89**	81	40
Incobotulinum-toxinA	XEOMIN INJ 100UNIT	–	–	–	–	<5	<5	–	–	**<5**	**<5**	–	–
Incobotulinum-toxinA	XEOMIN INJ 50 UNIT	–	–	–	–	<5	<5	–	–	**<5**	**<5**	–	–
Onabotulinum-toxinA	BOTOX INJ 100UNIT	332	143	388	174	449	161	292	132	**1,461**	**395**	405	199
Onabotulinum-toxinA	BOTOX INJ 200UNIT	32	13	106	25	65	35	102	39	**305**	**94**	62	35
Onabotulinum-toxinA (Cosmetic)	BOTOX COSMET INJ 100UNIT	10	<5	14	5	10	<5	<5	<5	**36**	**8**	11	6
Onabotulinum-toxinA (Cosmetic)	BOTOX COSMET INJ 50UNIT	<5	<5	–	–	–	–	<5	<5	**<5**	**<5**	<5	<5
Rimabotulinum-toxinB	MYOBLOC INJ 10000/2	<5	<5	<5	<5	–	–	–	–	**<5**	**<5**	–	–
Rimabotulinum-toxinB	MYOBLOC INJ 2500/0.5	–	–	<5	<5	<5	<5	<5	<5	**<5**	**<5**	–	–
Rimabotulinum-toxinB	MYOBLOC INJ 5000/ML	<5	<5	<5	<5	<5	<5	<5	<5	**11**	**<5**	<5	<5
Total	**Total**									**2,620**	**613**	**710**	**303**

Botulinum toxin - CPT

CLAIMS

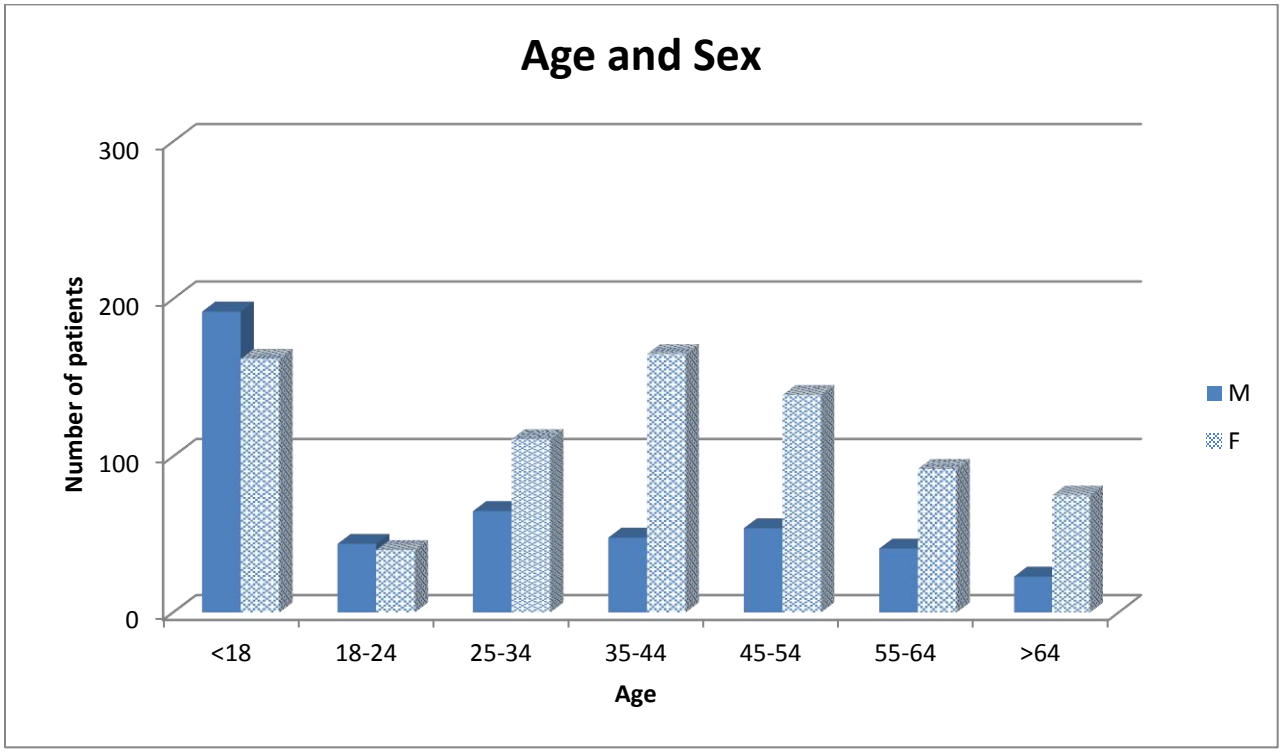
CPT CODE	PROCEDURE DESCRIPTION	2014 CLAIMS	2014 PATIENTS	2015 CLAIMS	2015 PATIENTS	2016 CLAIMS	2016 PATIENTS	2017* CLAIMS	2017* PATIENTS	ALL CLAIMS	ALL PATIENTS
J0585	BOTULINUM TOXIN TYPE A, PER UNIT	313	186	231	158	432	272	397	280	**1,373**	**568**
J0585	BOTULINUM TOXIN A (BOTOX) PER 1 UNIT	–	–	–	–	–	–	103	103	**103**	**103**
J0586	ABOBOTULINUM- TOXINA (DYSPORT) PER 5 UNITS	–	–	–	–	–	–	19	19	**19**	**19**
J0586	INJECTION, ABOBOTULINUM- TOXINA, 5 UNITS	106	84	58	48	116	78	91	68	**371**	**183**
J0587	BOTULINUM TOXIN TYPE B, PER 100 UNITS	<5	<5	<5	<5	<5	<5	8	6	**17**	**8**
J0587	RIMABOTULINUM-TOXINB (MYOBLOC) PER 100 UNITS	–	–	–	–	–	–	5	<5	**5**	**<5**
J0588	INCOBOTULINUM-TOXINA, 1 UNIT	–	–	–	–	–	–	–	–	–	–
Total	**Total**									**1888**	**≤784**

Note: Patients could meet Rx, Rx + CPT, or CPT criteria on different treatment dates

Total unique number of patients = 1251

- Most patients received Botox and Dysport

b) AGE AND SEX of patients for whom there were claims for botulinum toxin products.



BOTULINUM TOXIN - ALL PATIENTS

TOTAL PATIENTS 2014-2017

AGE*	M	F	Total	Female patients as percentage of total patients in age group
<18	192	162	354	46%
18-24	44	40	84	48%
25-34	65	111	176	63%
35-44	48	165	213	77%
45-54	54	139	193	72%
55-64	41	92	133	69%
>64	23	75	98	77%
TOTAL	467	784	1251	

* Age at first claim.

- 354/1251 (28%) are pediatric patients
- The number of female patients far outweigh male patients in all categories >25 (accounting for 63-77% of the patients in each age group) which raises the questions whether prevalence of approved uses is higher in females or whether these products are possibly being used for cosmetic reasons.

The purpose of this review is on pediatric use and this is beyond the scope of this review. Based on this data, we recommend reviewing use in adults as well.

c) The number of patients that received botulinum toxin that had select diagnosis codes or relevant CPT codes submitted

The number of patients that received botulinum toxin that had select diagnosis codes or relevant CPT codes submitted. Potential diagnosis codes were identified for drooling and spasticity defined as follows:

Drooling
K11.7 Disturbance of salivary secretion
CPT 64611 (chemodenervation …salivary gland)

Spasticity
G80* Cerebral palsy
- G80.0 Spastic quadriplegic cerebral palsy
- G80.1 Spastic diplegic cerebral palsy
- G80.2 Spastic hemiplegic cerebral palsy
- G80.3 Athetoid cerebral palsy
- G80.4 Ataxic cerebral palsy
- G80.8 Other cerebral palsy
- G80.9 Cerebral palsy, unspecified

M62.4* Contracture of muscle

M62.83 Muscle spasm
- M62.830 …… of back
- M62.831 …… of calf
- M62.838 Other muscle spasm

M21.6X9 Other acquired deformities of unspecified foot

G25.89 Other specified extrapyramidal and movement disorders

G81.1 Spastic hemiplegia
- G81.10 …… affecting unspecified side
- G81.11 …… affecting right dominant side
- G81.12 …… affecting left dominant side
- G81.13 …… affecting right nondominant side
- G81.14 …… affecting left nondominant side

Summary

- Only 419/1251 patients (33%) had one of these diagnosis codes submitted
- 171 of these patients are pediatric patients which will be summarized in the pediatric utilization section.
- Most of the diagnosis codes submitted were for cerebral palsy, muscle spasm, and spastic hemiplegia

- Drooling: No patients had a diagnosis code submitted for K11.7 Disturbance of salivary secretion and 9 patients had a CPT code submitted for CPT 64611 (chemodenervation …salivary gland)
- <5 patients that have Cerebral Palsy and a CPT code for CPT 64611 (chemodenervation …salivary gland)

Number of unique patients with any of these diagnosis codes submitted

AGE GROUP	Total	
	Patients	Percent
<18	171	40.8%
18-24	39	9.3%
25-34	60	14.3%
35-44	48	11.5%
45-54	40	9.5%
55-64	36	8.6%
>64	25	6.0%
Total	419	100.0%

BOTULINUM TOXIN - ALL PATIENTS

TOTAL PATIENTS 2014-2017

AGE GROUP	Cerebral palsy	Chemo-denervation salivary gland	Contracture of muscle	Muscle spasm	Other acquired deformities of unspecified foot	Other specified extrapyramidal and movement disorders	Spastic hemiplegia
<18	151	6	16	88	<5	0	9
18-24	27	0	7	22	<5	0	6
25-34	28	<5	6	43	<5	<5	10
35-44	17	<5	<5	38	0	<5	11
45-54	8	<5	5	32	<5	0	15
55-64	8	0	<5	32	0	0	14
>64	<5	0	<5	21	0	0	13
Total	≤244	9	44	276	5	5	78

* Age at first claim.

2) Pediatric utilization data

a) Table showing total utilization by prescription claims and CPT codes and the combined total unique patients

Botulinum toxin RX CLAIMS

AGENT	PRODUCT	2014		2015		2016		2017*		ALL		WiITH CPT	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Abobotulinum-toxinA	DYSPORT INJ 300UNIT	150	60	84	42	48	23	45	25	327	106	102	56
Abobotulinum-toxinA	DYSPORT INJ 500UNIT	133	46	70	27	36	19	29	14	268	70	64	31
Onabotulinum-toxinA	BOTOX INJ 100UNIT	47	26	38	18	27	11	25	12	137	47	47	25
Onabotulinum-toxinA	BOTOX INJ 200UNIT	–	–	<5	<5	9	5	20	11	30	16	6	5
Total										**762**	**168**	**219**	**83**

Botulinum toxin CPT CLAIMS

CPT CODE	PROCEDURE DESCRIPTION	2014		2015		2016		2017*		ALL	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
J0585	BOTULINUM TOXIN TYPE A, PER UNIT	35	26	42	25	41	29	47	38	165	83
J0585	BOTULINUM TOXIN A (BOTOX) PER 1 UNIT	–	–	–	–	–	–	13	13	13	13
J0586	ABOBOTULINUM-TOXINA (DYSPORT) PER 5 UNITS	–	–	–	–	–	–	9	9	9	9
J0586	INJECTION, ABOBOTULINUM-TOXINA, 5 UNITS	88	69	48	39	85	59	65	50	286	150
Total										**473**	**233**

Note: Patients could meet Rx, Rx + CPT, or CPT criteria on different treatment dates

Total unique pediatric patients = 354

b) AGE AND SEX of pediatric patients for whom there were claims for botulinum toxin products

BOTULINUM TOXIN - PEDIATRIC PATIENTS

TOTAL PATIENTS 2014-2017

AGE*	M	F
0	<5	5
1	8	16
2	16	11
3	17	17
4	16	23
5	13	16
6	8	15
7	10	6
8	12	8
9	8	9
10	7	14
11	6	10
12	8	6
13	10	12
14	7	6
15	<5	5
16	<5	7
17	5	6
Total	162	192

* Age at first claim.

c) The number of patients that received botulinum toxin that had select diagnosis codes or relevant CPT codes submitted

Definitions are included on page 25.

BOTULINUM TOXIN - PEDIATRIC PATIENTS

TOTAL PATIENTS 2014-2017

Age	Cerebral palsy	Chemodener-vation salivary gland	Contracture of muscle	Muscle spasm	Other acquired deformities of unspecified foot	Other specified extrapyramidal and movement disorders	Spastic hemiplegia
0	<5	0	0	0	0	0	0
1	7	0	0	8	0	0	0
2	9	0	<5	8	0	0	<5
3	14	<5	<5	10	0	0	0
4	18	<5	<5	11	0	0	0
5	17	0	<5	9	0	0	<5
6	15	0	<5	8	0	0	<5
7	6	0	0	<5	0	0	0
8	5	<5	0	5	<5	0	0
9	6	0	<5	5	0	0	0
10	10	0	<5	<5	0	0	0
11	9	0	<5	<5	0	0	0
12	5	<5	<5	<5	0	0	0
13	14	0	0	7	<5	0	0
14	<5	<5	0	0	0	0	<5
15	5	0	0	<5	0	0	0
16	<5	0	<5	<5	0	0	0
17	<5	0	0	<5	0	0	0
Total	151	6	16	88	<5	0	9

* Age at first claim.

- 171/354 pediatric patients that received botulinum toxin products had one of these diagnosis codes submitted
- Most of diagnosis codes were for cerebral palsy muscle spasm
- Drooling: 6/ 9 patients that had a CPT code submitted for CPT 64611 (chemodenervation …salivary gland) were pediatric patients

3) Pharmacy claims

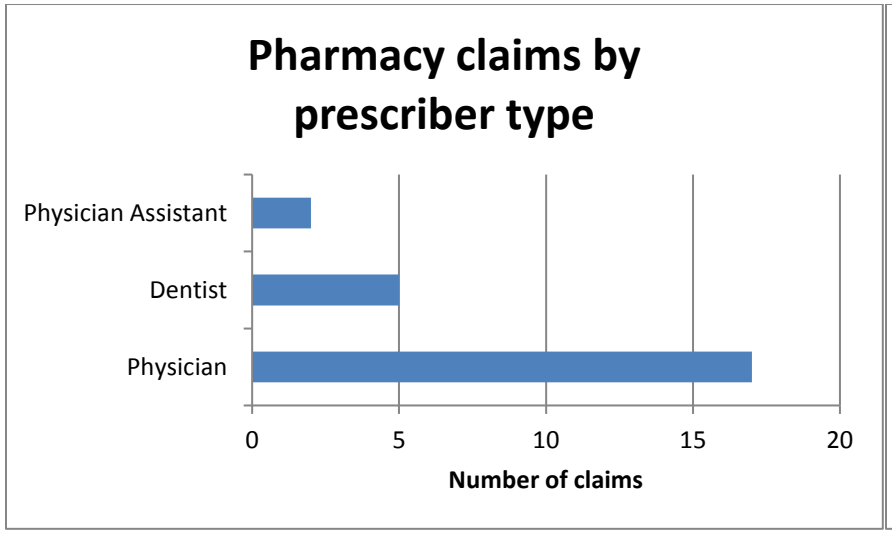
a) Table showing pharmacy claims for botulinum toxin products

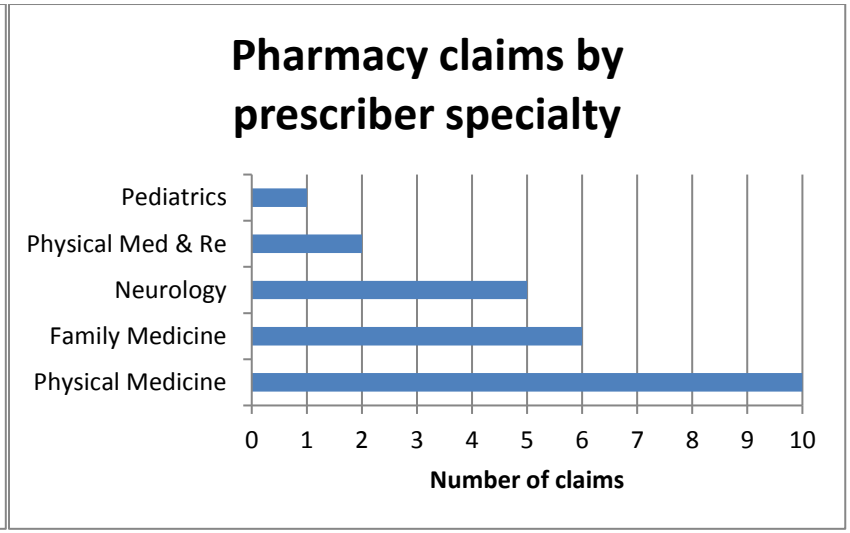
There were 24 pharmacy claims during this period.

Botulinum toxin - PHARMACY CLAIMS

		2014		2015		2016		2017*		ALL	
AGENT	PRODUCT	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
OnabotulinumtoxinA	BOTOX INJ 100UNIT	7	<5	<5	<5	–	–	<5	<5	10	
OnabotulinumtoxinA	BOTOX INJ 200UNIT	6	<5	8	<5	–	–	–	–	14	
Total	Total									**24**	**8**

b) Prescriber details





4) Frequency of fills compared to recommendations (no more frequently than every 3 months)

- 138 patients, 25 of them <18 years of age, have a claim sooner than 90 after a previous claim.
- 38 patients average fewer than 90 days across all fills

Conclusions

AbobotulinumtoxinA (Dysport) is the only botulinum toxin product that is FDA-approved for use in spasticity in pediatrics and this is limited to lower limb spasticity. The AAN and Child Neurological Society recommend botulinum toxin A for localized or segmental spasticity as an effective and generally safe treatment, and states insufficient evidence for botulinum B.[33,36] Botulinum toxin is not recommended for generalized spasticity. Sialorrhea is an off-label use of all botulinum toxin products. Based on the AAN recommendation, A/Abo, A/Ona, and B/Rima could potentially be effective. It is important to consider that this is a temporary treatment option and benefits need to be weighed against the potential serious adverse events.[48,49]

For products that include dosing information for use in spasticity in product labeling or Lexicomp, dosing more frequently than every 3 months is not recommended. Based on Canadian product labeling information, there appears to be some scenarios where it may be clinically indicated to repeat every 2 months. Some patients may also have a longer duration of response.

Appendix 1 – Systematic Reviews

Table 1. Cochrane Systematic Reviews

Authors	Title	Objectives	Main results	Conclusions
Ade-Hall R & Moore P (2000)[44]	Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy	"To determine whether botulinum toxin (BtA) is an effective and safe treatment for lower limb spasticity in children with cerebral palsy. Functional outcomes are of particular interest."	"Three eligible studies were found each with small numbers of subjects. They were short term, used single injection sessions with follow-up of between 4 and 26 weeks. One study (Koman), of twelve ambulant children, compared BtA with injection of a placebo and found non-significant improvements in gait in the BtA group compared to the placebo group. Two studies (Corry 1998, Flett 1999) compared BtA with the use of casts. Each included 20 ambulant children and found improvements in gait, range of ankle movement and muscle tone in both the BtA and cast groups . However there were no significant differences between the groups in either trial. One of these trials (Flett 1999) also assessed motor function using the gross motor function measure (GMFM) (Russell 1989) and found significant improvements in each group compared to baseline but no significant differences between the groups. The other trial (Corry 1998) performed 3D gait analysis on those children able to co-operate. Maximal plantar flexion and maximal dorsiflexion during walking were both found to be significantly greater in the BtA group compared to the cast group. In all other dimensions there were no significant differences between the groups."	"This systematic review has not revealed strong controlled evidence to support or refute the use of BtA for the treatment of leg spasticity in cerebral palsy. Ongoing randomised controlled trials are likely to provide useful data on the short term effects of BtA for leg spasticity. Future research should also assess the longer term use of BtA. Ideally studies should be pragmatic in their approach to dose and distribution of toxin to reflect practise. Outcome measures assessing function and disability would give the most useful information."
Hoare BJ, et al. (2010)[47]	Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE)	"To assess the effectiveness of injections of BoNT-A or BoNT-A and occupational therapy in the treatment of the upper limb in children with CP."	"Ten trials met the inclusion criteria. PEDro quality ratings ranged from 6/10 to 10/10. Concentration of BoNT-A ranged from 50U/1.0ml to 200U/1.0ml saline with doses of 0.5U to 16U/kg body weight and total doses of 220 to 410 Units (Botox®). A combination of BoNT-A and occupational therapy is more effective than occupational therapy alone in reducing impairment, improving activity level outcomes and goal achievement, but not for improving quality of life or perceived self-competence. When compared with placebo or no treatment, there is moderate evidence that BoNT-A alone is not effective."	"This systematic review found high level evidence supporting the use of BoNT-A as an adjunct to managing the upper limb in children with spastic CP. BoNT-A should not be used in isolation but should be accompanied by planned occupational therapy. Further research is essential to identify children most likely to respond to BoNT-A injections, monitor longitudinal outcomes, determine timing and effect of repeated injections and the most effective dosage, dilution and volume schedules. The most effective adjunct

Authors	Title	Objectives	Main results	Conclusions
				therapies including frequency and intensity of delivery also requires investigation."
Walshe M, et al. (2012)[12]	Interventions for drooling in children with cerebral palsy	"(1) To evaluate the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with cerebral palsy. (2) To provide the best available evidence to inform clinical practice. (3) To assist with future research planning." "Only randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were included"	"Six studies were eligible for inclusion in the review. Four of these studies were trials using botulinum toxin-A (BoNT-A) and two were trials on the pharmacological interventions, benztropine and glycopyrrolate. No RCTs or CCTs were retrieved on surgery, physical, oro-motor and oro-sensory therapies, behavioural interventions, intra-oral appliances or acupuncture. In the studies eligible for review, there was considerable heterogeneity within and across interventions and a meta-analysis was not possible. A descriptive summary of each study is provided. All studies showed some statistically significant change for treatment groups up to 1 month post intervention. However, there were methodological flaws associated with all six studies."	"It was not possible to reach a conclusion on the effectiveness and safety of either BoNT-A or the pharmaceutical interventions, benztropine and glycopyrrolate. There is insufficient evidence to inform clinical practice on interventions for drooling in children with CP. Directions for future research are provided." "Adequately powered well designed trials are required across all interventions. In addition to using sensitive measures looking at change in salivary flow, measures are needed that examine client and carer satisfaction, changes in quality of life, psychological well being and in unwanted symptoms associated with drooling."
Gray K, et al. (2014)[50]	Interventions for congenital talipes equinovarus (clubfoot)	"To evaluate the effectiveness of interventions for CTEV."	"We identified 14 trials in which there were 607 participants; one of the trials was newly included at this 2014 update. The use of different outcome measures prevented pooling of data for meta-analysis even when interventions and participants were comparable. All trials displayed bias in four or more areas. One trial reported on the primary outcome of function, though raw data were not available to be analysed. We were able to analyse data on foot alignment (Pirani score), a secondary outcome, from three trials. Two of the trials involved participants at initial presentation. One reported that the Ponseti technique significantly improved foot alignment compared to the Kite technique. After 10 weeks of serial casting, the average total Pirani score of the Ponseti group was 1.15 (95% confidence interval (CI) 0.98 to 1.32) lower than that of the Kite group. The second trial found the Ponseti technique to be superior to a traditional technique, with average total Pirani scores of the Ponseti participants 1.50 lower (95% CI 0.72 to 2.28) after serial casting and	"From the limited evidence available, the Ponseti technique produced significantly better short-term foot alignment compared to the Kite technique and compared to a traditional technique. The quality of this evidence was low to very low. An accelerated Ponseti technique may be as effective as a standard technique, according to moderate quality evidence. Relapse following the Kite technique more often led to major surgery compared to relapse following the Ponseti technique. We could draw no conclusions from other included trials because of the limited use of validated outcome measures and lack of available raw data. Future randomised controlled trials should address these issues."

Authors	Title	Objectives	Main results	Conclusions
			Achilles tenotomy. A trial in which the type of presentation was not reported found no difference between an accelerated Ponseti or standard Ponseti treatment. At the end of serial casting, the average total Pirani scores in the standard group were 0.31 lower (95% CI -0.40 to 1.02) than the accelerated group. Two trials in initial cases found relapse following Ponseti treatment was more likely to be corrected with further serial casting compared to the Kite groups which more often required major surgery (risk difference 25% and 50%). There is a lack of evidence for different plaster casting products, the addition of botulinum toxin A during the Ponseti technique, different types of major foot surgery, continuous passive motion treatment following major foot surgery, or treatment of relapsed or neglected cases of CTEV. Most trials did not report on adverse events. In trials evaluating serial casting techniques, adverse events included cast slippage (needing replacement), plaster sores (pressure areas) and skin irritation. Adverse events following surgical procedures included infection and the need for skin grafting."	
Synnot A, et al. (2017)[11]	Interventions for managing skeletal muscle spasticity following traumatic brain injury	To assess the effects of interventions for managing skeletal muscle spasticity in people with TBI. "One study included was in children/young people aged 4-18 years with traumatic brain injury and with 'mild to severe spastic tetraparesis' (weakness) in all limbs (n=25). They compared pseudoelastic orthosis versus traditional (static) splint for spasticity in people with traumatic brain injury." (not botulinum toxin) The Cochrane authors graded the quality of the evidence as very low (using GRADE).	"We included nine studies in this review which involved 134 participants with TBI. Only five studies reported between-group differences, yielding outcome data for 105 participants with TBI. These five studies assessed the effects of a range of pharmacological (baclofen, botulinum toxin A) and non-pharmacological (casting, physiotherapy, splints, tilt table standing and electrical stimulation) interventions, often in combination. The studies which tested the effect of baclofen and tizanidine did not report their results adequately. Where outcome data were available, spasticity and adverse events were reported, in addition to some secondary outcome measures. Of the five studies with results, three were funded by governments, charities or health services and two were funded by a pharmaceutical or medical technology company. The four studies without useable results were funded by pharmaceutical or medical technology companies. It was difficult to draw conclusions about the effectiveness of these interventions due to poor reporting, small study size and the fact that participants	"The very low quality and limited amount of evidence about the management of spasticity in people with TBI means that we are uncertain about the effectiveness or harms of these interventions. Well-designed and adequately powered studies using functional outcome measures to test the interventions used in clinical practice are needed."

Authors	Title	Objectives	Main results	Conclusions
			with TBI were usually only a proportion of the overall total. Meta-analysis was not feasible due to the paucity of data and heterogeneity of interventions and comparator groups. Some studies concluded that the intervention they tested had beneficial effects on spasticity, and others found no difference between certain treatments. The most common adverse event was minor skin damage in people who received casting. We believe it would be misleading to provide any further description of study results given the quality of the evidence was very low for all outcomes."	

Table 2. Other Reviews included in the Cochrane Library: Centre for Reviews and Dissemination (CRD): Systematic reviews that meet the criteria for inclusion on *Database of Abstracts of Reviews of Effects* (DARE).

Authors	Title	Objectives	Main results	Conclusions
Ryll U, et al. (2011)[45] *(CRD Provisional abstract)*	Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review	"To assess treatment effects of botulinum toxin type A (BoNT-A) on walking of children with leg spasticity due to cerebral palsy (CP) compared with usual care."	"Eight trials were included. Trials comparing BoNT-A plus usual care or physiotherapy versus usual care or physiotherapy alone showed moderate evidence for functional outcomes at 2 to 6, 12, and 24 weeks follow-up in favour of BoNT-A. Studies comparing BoNT-A versus casting showed strong evidence for no difference in effects between these interventions. A limitation of our review was the exclusion of studies not published in English, Dutch, or German. The heterogeneity of the included studies, especially for outcome measures and follow-up assessments, prompted us to refrain from statistical pooling, which might also be considered a limitation."	**"Interpretation** The use of BoNT-A with usual care or physiotherapy seems to improve walking of children with CP, but results should be appraised carefully owing to the limited quality of included trials."
Vashishta R, et al.(2013)[48] *(CRD Provisional abstract)*	Botulinum toxin for the treatment of sialorrhea: a meta-analysis.	"Botulinum toxin has emerged as an effective approach for the management of sialorrhea. This study presents a critical literature review and meta-analysis to determine the impact of botulinum toxin on drooling severity in patients with sialorrhea."	"Eight studies involving 181 patients (83 placebo; 98 active) were included in the analysis. Botulinum toxin was found to significantly decrease the severity of drooling in patients with sialorrhea (standardized mean difference [SMD], -1.54; 95% confidence interval [CI], -2.05 to -1.04; P = .06; I (2) = 48%) when compared with placebo control using random effects models. The effect was significant in both adult (SMD, -1.29; 95% CI, -1.88 to -0.71) and pediatric (SMD, -1.84; 95% CI, -2.67 to -1.00) populations. Both botulinum toxin A (SMD, -1.53; 95% CI, -2.27 to -0.79) and B (SMD, -1.56; 95% CI, -2.32 to -0.79) produced similar effects. Botulinum toxin doses greater than 50 U (SMD, -3.81; 95% CI, -6.19 to -1.43) produced much stronger effects compared with doses less than or equal to 50 U (SMD, -1.32; 95% CI, -2.28 to -0.36)."	"Botulinum toxin is a clinically effective therapy that improves drooling severity in patients with sialorrhea. Future studies will need to further evaluate the technique and examine dosages required to achieve optimal outcomes."

Authors	Title	Objectives	Main results	Conclusions
Koog YH & Min BI (2010)[46] *(CRD Provisional abstract)*	Effects of botulinum toxin A on calf muscles in children with cerebral palsy: a systematic review.	"To assess the efficacy of botulinum toxin A injection for the management of spastic calf muscles in children with cerebral palsy."	"Fifteen studies met our inclusion criteria. When botulinum injection was compared with a non-sham control, it was found to be effective at improving calf muscle tone (one month: -2.73 (confidence interval (CI) -3.42 to -2.04), three months: -1.72 (-2.68 to -0.76)), passive ankle range of motion (one month: 3.29 (CI 2.52 to 4.05), three months: 1.00 (CI 0.44 to 1.56)) and gait speed (one month: 0.91 (CI 0.29 to 1.53), three months: 0.61 (CI 0.01 to 1.21)) for four months, as well as Gross Motor Function Measure (2.02 (CI 1.30 to 2.75)) for two months. When compared with sham injection, botulinum injection was only effective on Gross Motor Function Measure (0.98 (CI 0.28 to 1.69)) after four months."	"Although we found evidence supporting the efficacy of botulinum toxin A in studies comparing botulinum injection with non-sham controls, we did not find clear evidence of support in studies comparing botulinum injection with sham injection."
Rodwell K, et al. (2012) *(CRD Provisional abstract)*	Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review	"The aim of this paper was to systematically review the efficacy and safety of botulinum toxin (BoNT) injections to the salivary glands to treat drooling in children with cerebral palsy and neurodevelopmental disability."	"Sixteen studies met inclusion criteria. Three outcome measures support the effectiveness of BoNT for drooling. One RCT found an almost 30% reduction in the impact of drooling on patients' lives, as measured by the Drooling Impact Scale (mean difference −27.45; 95% confidence interval [CI] −35.28 to −19.62). There were sufficient data to pool results on one outcome measure, the Drooling Frequency and Severity Scale, which supports this result (mean difference −2.71; 95% CI −4.82 to −0.60; p<0.001). There was a significant reduction in the observed number of bibs required per day. The incidence of adverse events ranged from 2 to 41%, but was inconsistently reported. One trial was terminated early because of adverse events."	**"Interpretation** BoNT is an effective, temporary treatment for sialorrhoea in children with cerebral palsy. Benefits need to be weighed against the potential for serious adverse events. More studies are needed to address the safety of BoNT and to compare BoNT with other treatment options for drooling."
Sakzewski L, et al. (2014)[55]	Efficacy of Upper Limb Therapies for Unilateral Cerebral Palsy: A Meta-analysis	"…to systematically review the efficacy of nonsurgical upper limb therapies for children with unilateral cerebral palsy."	"Forty-two studies evaluating 113 UL therapy approaches (N = 1454 subjects) met the inclusion criteria. Moderate to strong effects favoring intramuscular injections of botulinum toxin A and occupational therapy (OT) to improve UL and individualized outcomes compared with OT alone were identified. Constraint-induced movement therapy achieved modest to strong treatment effects on improving movement quality and efficiency of the impaired UL compared with usual care. There were weak treatment effects for most outcomes when constraint therapy was compared with an equal dose (amount) of bimanual OT; both yielded similar improved outcomes. Newer interventions such as action observation training and mirror therapy should be viewed as experimental."	"There is modest evidence that intensive activity-based, goal-directed interventions (eg, constraint-induced movement therapy, bimanual training) are more effective than standard care in improving UL and individualized outcomes. There is little evidence to support block therapy alone as the dose of intervention is unlikely to be sufficient to lead to sustained changes in UL outcomes. There is strong evidence that goal-directed OT home programs are effective and could supplement hands-on direct therapy to achieve increased dose of intervention."

Appendix 2 – Utah Poison Control Center: Botulinum Toxin Exposures

Utah Poison Control Center
Botulinum Toxin Type A Exposures
January 1, 2013 – December 8, 2017

I. Case Summaries

Year	Reason	Cases
2013		2
	Possible ADR	1
	Therapeutic error	1
2014		3
	Possible ADR	3
2015		3
	Possible ADR	2
	Occupational eye	1
2016		3
	Possible ADR	3
2017		5
	Possible ADR	4
	Occupational eye	1
Total		**16**

II. Case Highlights

A. Age and Gender
- Mean age 42 years
- 15 females age 23-58
- 1 male age 40

B. Common clinical effects
- Gastrointestinal
  - nausea: 5
  - abdominal pain
  - diarrhea
  - blood in stool
- Neurologic
  - weakness: 5
  - throat irritation/difficulty swallowing/tongue swelling: 3
  - fatigue: 3

    - eye irritation: 2
    - droopy eye lids/eyes not working properly: 2
    - headache
    - anxious
    - dizziness
- Cardio/pulmonary
    - shortness of breath/difficulty breathing/chest tightness: 5
    - palpitations
- Musculoskeletal
    - muscle tightness/pain: 3
    - numbness/tingling
- Other
    - flu-like illness: 2
    - diaphoresis
    - fever
    - face swollen
    - swollen lymph nodes

C. Time course

- All but 3 cases involved concern for adverse effect following injection
- Time to presentation for possible adverse effects ranged from 0.5 days to 1 month with a mean of 10 days
- All but 3 patients sought medical treatment in a hospital or clinic.
- All but 1 patient was discharged from emergency department/clinic. One patient was admitted overnight for observation
- Viral illness was suspected in a number of the cases

Appendix 3 – Utah Poison Control Center: Botulism Exposures

Utah Poison Control Center
Botulism Exposures
January 1, 2008 – December 8, 2017

Botulism antitoxin is available through the Centers for Disease Control and Prevention (CDC) on request of the state health department. Decisions to administer antitoxin are made in consultation between treating clinician, state health department and CDC. Infant botulism is treated with botulism immune globulin available through the California Department of Health at the request of the treating physician. Botulism is fairly rare. All cases per year had the same source.

I. Case Summary

Year	Type	Source	Cases
2008	Infant	Environmental	1
2011	Adult	Homemade alcohol	6
2015	Adult	Beets	2
Total			**9**

II. Case Highlights

A. Age and Gender
- One infant (6 months)
- Adults age range 24-66 years
- 2 /9 female

B. Common clinical effects
- all adults with documented dysphagia
- 4/9 complained of dizziness
- 4/9 muscle weakness
- 6/9 slurred speech
- 3/9 blurred vision

C. Respiratory Support
- 4/9 required mechanical ventilation
- 1 required a tracheostomy

D. Hospital course
- 8/9 admitted to critical care unit – remaining patient to medical floor

- 3/9 were coded as having a major effect (life-threatening); remainder coded as moderate effect
- 5/9 had hospital lengths of stays of ~ 5 days
- 2/9 with hospital lengths of stay of 10 days
- 1 was hospitalized in acute care for 25 days followed by approximately 1 month in rehab
- 1 had length of stay of ~ 31 days
- Many had residual symptoms after discharge that resolved very slowly

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